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Multiattribute Approach to the Assessment of Health-Related Quality of Life: Health Utilities Index

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INTRODUCTION

As survival rates among children with cancer have increased, often spectacularly, new issues have become important. Attention is now focused on investigating innovations in treatments that can reduce the toxicity and health-related quality-of-life (HRQL) burdens of treatment without compromising survival. Similarly, attention is also focused on the sequelae of cancer and its treatments and on the discovery of treatments that generate fewer burdens among survivors.

The assessment of HRQL among children during the treatment process itself and among survivors of cancer in children is intrinsically important. Quality and quantity of life are among the most fundamental objectives of treatment. Instrumentally, measures of HRQL are required to enable pediatric oncologists to assess new treatment protocols that are designed to lessen toxicity and sequelae.

The assessment of HRQL is a relatively new field. Kirshner and Guyatt [1] distinguish three basic purposes for assessing HRQL: discrimination, evaluation, and prediction. Discrimination refers to the use of a measure cross-sectionally at a point in time to compare groups. In the context of the late-effects literature, the burden of morbidity among survivors might be compared among diseases. Evaluation refers to the assessment of change in HRQL within people over time in longitudinal studies. Thus, a measure of HRQL might be used to compare changes in toxicity between two different treatment protocols in a clinical trial. Prediction refers to the use of a measure to predict the score from another measure at the same point in time (for instance, substitution of short form for long form of an instrument) or to predict outcome in the future. Evidence on the use of HRQL measures at diagnosis as predictors of survival is found in reports by Coates et al. [2] and Clinch [3]. In the context of pediatric oncology, we are interested mainly, but not exclusively, in discriminative and evaluative uses of HRQL measures.

There are a number of taxonomies of HRQL measures. One approach classifies measures as specific measures, which apply to particular populations; or generic measures, which apply to virtually any population [4]. Specific measures focus only on those aspects of HRQL that are important to patients with a particular disease or problem. In general, specific measures do not allow for broad comparisons. Because generic measures apply to virtually any population, they cover a broad array of dimensions of HRQL and allow for broad comparisons. Generic measures, however, may be somewhat coarse and blunt compared with specific measures. In general, specific and generic measures provide complementary types of information, and some authorities recommend that both types of measures be employed routinely [5].

This paper discusses one approach to the assessment of HRQL in children with cancer–a generic, multiattribute approach known as the Health Utilities Index (HUI). Evidence on the performance of HUI in pediatric oncology settings for both discriminative and evaluative purposes is summarized and discussed. Finally, ideas on the role of HUI in HRQL studies in childhood cancer are presented.

MATERIALS AND METHODS

In adult medicine, an array of specific and generic measures is available. Unfortunately, relatively few measures are available in pediatrics [6]. In pediatric oncology, specific measures include the work of Lansky, Goodwin and Boggs, Feeny et al., and Deasy-Spinetta and Spinetta [7–11], and generic measures include the HUI. Of course, a number of additional specific and generic measures for childhood cancer are currently under development.

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HUI

The HUI is an example of a generic, multiattribute approach to the assessment of health status and HRQL [12,13]. In the multiattribute approach, health status is defined as being comprised of a number of dimensions (or characteristics, or domains, or attributes). Levels within each attribute, from normal (or even supranormal) to severely compromised, are then defined. Multiattribute approaches thus provide a comprehensive but compact way to describe the health status of an individual at a point in time. Multiattribute systems provide a ''holistic'' description of subjects and, thus, facilitate the examination of multiple sequelae and varying levels of severity of problems.

The second component of the multiattribute approach is a system that converts the health-state description into a HRQL score, usually on the conventional dead = 0.00 and perfect health = 1.00 scale. This scale permits the integration of mortality and morbidity, allows broad comparisons, and greatly facilitates the conduct of cost-utility analyses.

The HUI Mark 1 (HUI1) system was developed for the evaluation of outcomes of neonatal intensive care [14,15]. Like survivors of childhood cancer, very-low-birthweight survivors have various types of sequelae with varying degrees of severity of impairment.

HUI Mark 2 was developed specifically for childhood cancer [12,16–19] and is comprised of seven attributes–sensation (vision, hearing, and speech), mobility, emotion, cognition, self care, pain, and fertility–with three to five levels per attribute. HUI2 describes 24,000 unique health states (the number of unique combinations of seven attributes with three to five levels per attribute).

A multiplicative, multiattribute utility function has been estimated for the HUI2 system [20,21]. The function is based on preference measurements from a random sample of 203 general public parents in Hamilton, Ontario, Canada.

The attributes in HUI2 were chosen on the basis of work by Cadman and colleagues [22,23]. Those authors conducted a thorough search of the then existing literature on the assessment of health status and compiled a list of 15 attributes. A random sample of general public parents and children was then asked to rate the importance of each of these attributes. Cadman et al. then selected the six most important attributes as the basis of their system. HUI2 added fertility to the set of six and elaborated on the number of levels per attribute. A health state in HUI2 is then defined as one level per attribute, represented as a seven-element vector.

The HUI3 system was developed initially for use in the 1990 Ontario Health Survey. HUI3 was based closely on HUI2 and was designed for use both in population health and clinical studies. HUI3 is comprised of eight attributes–vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain–with five to six levels per attribute. HUI3 describes 972,000 health states. Multiplicative and multilinear utility functions for the HUI3 are being developed currently.

HUI2 and HUI3 adopt a ''within-the-skin'' definition of health status, i.e., the extent to which one's health status permits one to engage in the activities one chooses to engage in or the extent to which health status inhibits such engagement. The focus is on capacity rather than performance. Performance reflects capacity, opportunity, and preferences.

HUI2 and HUI3 provide complementary sets of information. Together, the two systems include ten dimensions of health status. Although there is considerable overlap between the two systems, the constructs used for some attributes (for instance, emotion) differ between the two systems. In addition, dexterity is exclusive to HUI3, whereas self care and fertility are exclusive to HUI2. Thus, in general, it is wise to use both systems in a study.

One of the advantages of HUI is the availability of data on population norms. HUI3 has been used in four major population health surveys in Canada: the 1990 Ontario Health Survey (n = 61,239), the 1991 Statistics Canada General Social Survey (n = 11,567), the 1994 and on-going National Population Health Survey (n = 19,600), and the 1994 and on-going National Longitudinal Survey of Children and Youth that will provide data on 22,831 children (scheduled for public release in the Spring of 1998).

Questionnaires for collecting HUI data in clinical and population health surveys have been developed. In addition, there are algorithms for converting responses into health states, as defined in the HUI2 and HUI3 systems.

Another advantage of HUI is that it facilitates the use of multiple assessors of health status at a point in time. In pediatrics in general and pediatric oncology in particular, patients are often too young to provide reliable and valid information on their own health status. In addition, during some phases of therapy, children may be too ill to complete HRQL instruments. Therefore, it is often necessary to rely on proxy respondents, such as parents, nurses, physicians, or other health-care professionals. It is important to recognize that the use of proxy respondents can introduce bias into the assessment of health status, especially for subjective phenomenon, such as pain and emotion. The viewpoint from which health status is assessed needs to be kept consistent throughout a study and must be made explicit. Nonetheless, proxy respondents provide valuable information on health status.

Performance Characteristics for Measures of HRQL

There are a number of criteria relevant to the assessment of HRQL measures. These include acceptability,

burden, reliability, validity, responsiveness, interpretability, and usefulness. Acceptability may be assessed by the degree of compliance with the instrument by subjects, parents, and health-care professionals. Burden refers to how onerous application of the measure is to respondents in terms of time, effort, and potential upset. Reliability includes the extent to which repeat measurements among stable subjects provide the same answer. Reliability can also refer to the degree of agreement among observers. Validity refers to the extent to which the measure captures what it was designed to measure. Given the lack of a gold standard in HRQL measurement, analysts rely on the accumulation of evidence that conforms to a priori expectations as evidence for validity. Interpretability refers to the meaningfulness and understandability of the HRQL information and scores. Usefulness refers to the extent to which HRQL measures provide input into clinical management, clinical policy, and resource-allocation decision making. Evidence for each of these criteria for HUI in pediatric oncology (and related applications) are discussed briefly below.

RESULTS

Acceptability and Burden

HUI appears to be acceptable to a variety of groups. Parents appear to understand and are able to complete questionnaires based on HUI2 and/or HUI3, as evidenced by its use in studies on children with brain tumors [18], patients in pediatric intensive care units [24], parents of very-low-birthweight children who are now teenagers, and controls [25] as well as the use of HUI3 in a number of population health surveys, as mentioned above. HUI is also acceptable to children, as evidenced by its use in long-term follow-up of very-low-birthweight children and controls [25].

Questionnaires designed to obtain data for HUI2/HUI3 appear to generate little burden for respondents, and completion times for self-administered versions of the questionnaire are in the 5–10 minute range. Self completion, typically without assistance, appears to be feasible for respondents with a third-grade reading level or higher.

Reliability

Intrarater and intramode (same respondent using the same questionnaire) agreement for HUI3 have been investigated by Statistics Canada in the context of the 1991 General Social Survey. A test-retest study with a 1-month interval was carried out on a subsample of 506 respondents [26]. Reliability was examined on a question-by-question basis, on the assignment of levels by attribute, and on the global utility score. The percent agreement was very high, ranging from 82% to 99%. Kappa statistics for agreement on levels for six of the eight attributes varied from 0.50 to 0.73. The intraclass correlation coefficient for the global utility scores between the two assessments was 0.77.

TABLE I. Comparison of Standard-Risk Acute Lymphoblastic Leukemia and Brain Tumor Survivors†

	SR-ALL (%)	BT (%)
Attributes affected (no.)*		
0	60	20
1	32	10
2+	8	70
Health states (no.)	7	9
Mean global utility score (SD)**	0.96 (0.07)	0.79 (0.17)

†Standard-risk acute lymphoblastic leukemia (SR-ALL; n = 25) [19] versus brain tumors (BT; n = 10) from assessments 2A of Barr et al. [18].
*$\chi^2 = 14.4$; $P < 0.001$.
**$P = 0.015$.

Interrater reliability for HUI2 was investigated by Gemke et al. [24] in a study that involved 254 children who were admitted to pediatric intensive care for a variety of indications. Health status was evaluated independently by parents, the attending clinician, and the authors of the paper. The Spearman-Rank correlation coefficients by attribute varied from 0.36 to 0.96. Among the 18 paired comparisons, Spearman-Rank correlation coefficients were $\geqslant 0.90$ for four pairs, $\geqslant 0.80$ but <0.90 for seven pairs, $\leqslant 0.70$ but <0.80 for three pairs, and <0.70 for four pairs. Barr et al. [18] provide further evidence of interrater reliability.

Validity

A number of studies provide evidence of construct validity. Table I provides a comparison of the health status and HRQL of survivors of standard-risk acute lymphoblastic leukemia (SR-ALL) and brain tumors in childhood, indicating, as one would expect, that brain tumor survivors suffer a greater burden of morbidity. The higher burden of morbidity is notable in the number of attributes affected (any impairment), the number of health states (unique, six-element vectors) it takes to describe each cohort of survivors, the mean global utility scores for the two groups, and the variability of the global utility scores for the two groups. Although 60% of SR-ALL survivors had perfect health (zero attributes affected), only 20% of brain tumor survivors enjoyed perfect health. Similarly, although only 8% of SR-ALL survivors had multiple sequelae in the form of two or more attributes affected, 70% of brain tumor survivors had such multiple sequelae. Furthermore, the burdens of morbidity for each group were in the attributes that one would expect. Brain tumor survivors had impairments in sensation, emotion, and cognition. The SR-ALL survivors with impairments had problems with cognition or emotion. It is also interesting to note that seven health

states were sufficient to describe the 25 SR-ALL survivors (0.28 health states per person in the cohort), but it took nine health states to describe the ten brain tumor survivors (0.90 health states per person).

The impression that emerges from these categorical data is that the variability in outcomes for brain tumor survivors is higher and that the brain tumor survivors suffer, on average, a greater burden of morbidity. This impression is reinforced by a comparison of the mean global utility scores and standard deviations for each group. The mean utility score for the SR-ALL survivors was 0.95, which is equal to the score for the control group (at 8 years of age) described by Saigal et al. [27]. The mean utility score for the brain tumor survivors was 0.79, implying that, as a group, these survivors suffered a similar (or even greater) burden of morbidity compared with extremely-low-birthweight survivors who had a mean utility score of 0.82 (assessed at age the age of 8 years) [27,28].

Further evidence of validity is provided by Saigal et al. [27,28], who compared extremely-low-birthweight survivors with controls; by Gemke and Bonsel [24] and Barr et al. [17], who compared SR-ALL with high-risk ALL survivors and with the general population; by Barr et al. [18], who compared brain tumor survivors with the general public; and by Feeny et al. [16], who compared high-risk ALL survivors with the general public [see also 12,19,29,30–35]. Evidence of validity from comparisons among groups (by age, education, income, and other factors) in population health surveys is found in the literature [36–39]. The health status of better educated people, as one would expect, compared favorably to that of the less well educated. A similar pattern was observed when health status was compared among income groups. Also as one would expect, health status declined with age.

Responsiveness

The HUI was shown to be responsive in a small study of 18 consecutive patients who were on maintenance therapy for ALL [40]. Children were assessed at each clinic visit by a nurse who was blinded to the stage of the treatment cycle and to methodological hypotheses, using HUI2 and HUI3. At week 1, patients had been off of all therapy for 6 days and were then given a 5-day course of corticosteroids, began oral mercaptopurine (MP) daily, and received vincristine with methotrexate intravenously. At week 2, patients were assessed again, were given methotrexate i.v., and continued oral MP. At week 3, patients were assessed and given a dose of methotrexate i.v. Data on the presence or absence of impairment in mobility, emotion, and pain–the attributes one would expect to be affected by therapy and, in particular, by steroids–are presented in Table II. At week 1, patients had few impairments, but, at week 2, approximately 50% had impairments in mobility and emotion, and over 70% experienced pain. The impression of a deterioration in health status from these categorical data is confirmed in Table III, in which single-attribute utility scores by week for mobility, emotion, and pain are reported. For instance, there are statistically significant differences in the mean utility scores for emotion between weeks 1 and 2 and between weeks 2 and 3 in the expected directions.

TABLE II. Acute Lymphoblastic Leukemia Study: Frequency of Impairments by Attribute (in Percent)

	Mobility[a]		Emotion		Pain	
Week	FF	AD	FF	AD	FF	AD
1	72	28	83	17	67	33
2	44	56	50	50	28	72
3	75	25	75	25	63	37

[a]FF, full function (level 1); AD, any disability (level other than level 1). Source: Barr et al. [40].

TABLE III. Acute Lymphoblastic Leukemia Study: Single-Attribute Scores (SD) by Week of Cycle*

Assessment	No.	Mobility	Emotion	Pain
Week 1	18	0.98 (0.04)	0.98 (0.05)	0.98 (0.02)
Week 2	18	0.96 (0.04)	0.89 (0.15)	0.91 (0.10)
Week 3	16	0.98 (0.04)	0.92 (0.16)	0.96 (0.08)

*The single-attribute utility scale for each attribute goes from level 1 (1.00) to the lowest level for that attribute (0.00). Source: Barr et al. [40].

TABLE IV. Acute Lymphoblastic Leukemia Study: Global Utility Scores by Week of Cycle*

Assessment	Utility score
Week 1	0.96
Week 2	0.86
Week 3	0.91

*Utility scores are on the conventional scale in which dead = 0.00, and perfect health = 1.00. The change in mean score between weeks 1 and 2 is statistically significant ($P = 0.0014$). Source: Barr et al. [40].

At week 1, it took eight health states to describe the 18 patients. At week 2, it took 14 health states, and, at week 3, it took nine heath states. Health states that were observed at week 2 but not at weeks 1 or 3 involved higher levels of morbidity in mobility, emotion, and pain. Table IV provides mean global utility scores by week. Again, the same pattern emerges: HRQL declines between weeks 1 and 2 and improves between weeks 2 and 3.

Interpretability

Categorical data on health status in HUI2 and HUI3 are readily interpretable. Data from studies for a variety of cancers in childhood, including ALL, brain tumors, neuroblastoma, and Wilms tumor, provide a basis for making comparisons and for understanding the meaning of the health status and HRQL information. The inter-

pretability of such data is enhanced by the use of HUI2/HUI3 in a number of other pediatric settings, including asthma, arthritis, intensive care, very low birthweight, and liver transplantation. Interpretability is also enhanced by the availability of data on population norms.

Usefulness

The use of HRQL measures can improve communication among health-care providers, patients, and their families [18]. We found that the routine use in the clinic of a 15-item questionnaire, which is sufficient to provide information to classify subjects in both the HUI2 and the HUI3 systems, affected positively the informational content of clinical encounters. The administration of the 15-item questionnaire in neurooncology clinics also revealed an under-recognized burden of pain both in adult and pediatric patients [41; see also 33].

DISCUSSION

Evidence to date indicates that HUI performs well as a measure of health status and HRQL in childhood cancer. HUI is acceptable to a wide variety of users and imposes minimal burdens. Like all measures of HRQL, its administration requires careful planning, a trained staff, and enthusiastic investigators who communicate the priority they place on HRQL information to respondents. Intrarater and interrater reliability appear to be more than acceptable. HUI was able to detect the kinds of differences between groups, among diseases, or comparing disease groups with population norms, which was expected. Like many other generic systems, HUI has also been able to reveal under-recognized burdens of morbidity.

It is useful to display data from HUI in a variety of forms. The categorical data on number of attributes affected, level of severity of impairments, and number of health states are valuable in creating a multidimensional picture of health status. The single-attribute utility functions and global utility scores afford the use of more powerful parametric statistical techniques. We have found that both the categorical descriptions and the utility scores are necessary to form a comprehensive understanding of the health status and HRQL of groups of patients.

CONCLUSIONS

Cancer in childhood affects a broad range of dimensions of health status. In addition, as in other pediatric settings, the assessment of HRQL in children is complicated by developmental changes [6,42]. What should be regarded as normal functional capacity changes systematically over time. Thus, the assessment of health status and HRQL in children with cancer is especially challenging.

The HUI provides a comprehensive but compact, generic measure of health status and HRQL that is applicable to cancer in childhood and pediatric health in general. HUI is also linked to rigorously specified and estimated scoring functions. In addition, there are abundant data on HUI both for particular groups and for population norms.

Evidence on the performance characteristics of HUI is accumulating. To date, HUI appears to be acceptable, imposes a low burden on the assessor, and is reliable, valid, responsive, and useful. HUI performs well for both discriminative and evaluative purposes. HUI complements more focused instruments that are relevant to particular age groups or types of childhood cancer and admits a variety of viewpoints for measurement.

In summary, HUI is a valuable tool for assessing health status and HRQL for children on therapy as well as in long-term follow-up. The use of HUI and other measures of HRQL will hasten learning on how to reduce toxicity and diminish sequelae for children with cancer.

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